DESCRIPTION

INJECTABLE COMPOSITION

Cross-Reference to Related Applications

[0001] This application is a continuation of U.S. Serial No. 09/563,969, filed May 3, 2000, which is a continuation of U. S. Serial No. 09/356,158, filed July 19, 1999, which is a continuation of U. S. Serial No. 08/979,836, filed November 26, 1997, which is a divisional of U. S. Serial No. 08/594,478, filed January 31, 1996, now U. S. Patent No. 5,196,125; which is a continuation of U. S. Serial No. 07/995,501, filed December 22, 1992, now abandoned.

Cross-Reference to Related Foreign Application

[0002] This application claims priority under 35 U.S.C. 119 to Australian Patent No. 6074, filed November 27, 1992.

[0003] This invention relates to a solution of paclitaxel having improved stability.

Background of the Invention

[0004] Paclitaxel is a compound extracted from the bark of a western yew, *Taxus brevifolia* and known for its antineoplastic activity. It is described for example in The Merck Index, Eleventh Edition 1989, monograph 9049.

[0005] In 1977, paclitaxel was chosen for development as an antineoplastic agent because of its unique mechanism of action and good cytotoxic activity against IP implanted D16 melanoma and the human X-1 mammary tumor xenograft. Paclitaxel is believed to function as a mitotic spindle poison and as a potent inhibitor of cell replication in vitro. Other mitotic spindle points (colchicine and podophyllotoxin) inhibit microtubule assembly. Paclitaxel employs a different mechanism of action since it appears to shift the equilibrium of polymerization/depolymerization toward polymer assembly and to stabilize microtubules against depolymerization under conditions which would cause rapid disaggregation of microtubules. The interference with the polymerization/depolymerization cycle in cells appears to interfere with both the replication and migration of cells.

[0006] After extensive preclinical screening in mouse tumor models, paclitaxel entered clinical trials in 1983. Over the past few years, paclitaxel has demonstrated good response rates in treating both ovarian and breast cancer patients who were not benefitting from vinca alkaloid or cisplatin therapy. It has also shown encouraging results in patients with other types of cancer including lung, melanoma, lymphoma, head and neck.

[0007] For further information, reference may be made to the U. S. National Cancer Institute's Clinical Brochure for Taxol, revised July 1991, and papers presented at the Second National Cancer Institute Workshop on Taxol and Taxus held in Alexandria, Virginia USA on September 23-24, 1992.

Brief Description of the Invention

[0008] It is a disadvantage of the known formulation that the paclitaxel therein degrades, with the result that the shelf life of the formulation is unsatisfactory, and there is therefore a need for a paclitaxel solution of improved stability.

[0009] Accordingly, in a general aspect the invention provides a solution containing paclitaxel, cremophor EL™ and ethanol, characterized in that the pH of the solution has been adjusted into the range 1 to 8 by addition of an acid.

[00010] Acids in the form of powders, for example citric acid, are preferred over those which contain water, for example sulfuric acid. The most preferred acid for use in accordance with the present invention is citric acid, but a wide range of acids may be used including the following:

Citric acid - monohydrous
Citric acid - anhydrous
Citric acid - hydrous
Acetic acid
Formic acid
Ascorbic acid
Aspartic acid
Benzene sulphonic acid

Benzoic acid

Hydrochloric acid

Sulphuric acid

Phosphoric acid

Nitric acid

Tartaric acid

Diatrizoic acid

Glutamic acid

Lactic acid

Maleic acid

Succinic acid

Detailed Description of the Illustrated Embodiments

[00011] Due to its limited solubility in water, Paclitaxel is usually prepared and administered in a vehicle containing cremophor EL™ (a polyethoxylated castor oil which acts as a solubilizer) and ethanol. A commercially available solution supplied by Bristol-Myers Squibb (BMS) is formulated with these components and has a pH of 9.1.

[00012] As indicated above, the invention essentially teaches addition of an acid to a paclitaxel formulation to adjust its pH into the range 1 to 8, preferable 5 to 7.

[00013] In a preferred procedure adopted by the applicant, which it will be clearly understood is non-limiting, the following steps were carried out:

Mixing Instructions

Solution 1

[00014] Citric acid was dissolved in absolute alcohol, using a ratio of 8 mls of absolute alcohol to 1 gram of citric acid, and the solution was stirred for fifteen (15) minutes.

Solution 2

[00015] Cremophor EL was weighed out into the main mixing vessel.

Solution 3

[00016] Solution 1 was added to solution 2, and the container used for solution 2 was washed with a minimum quantity of absolute alcohol to ensure complete transfer of the citric acid. Solution 3 was mixed and bubbled with nitrogen for at least 15 minutes. The paclitaxel was weighed out and slurried using absolute alcohol, using a ratio of 8 ml of absolute alcohol to 1 gm of paclitaxel. The slurried paclitaxel was added to solution 3 and the slurrying vessel was washed with a minimum quantity of absolute alcohol. Solution 3 was adjusted to 75% of required volume using absolute alcohol, and thoroughly stirred for at least 45 minutes until completely dissolved. Once completely dissolved, the volume was checked and made up as necessary with absolute alcohol and the final solution stirred for 5 minutes.

Example 1

[00017] A solution was prepared with the following formulation:

Formulation: (Sample 1)	
Cremophor EL	0.5 mL
Citric Acid (Anhydrous)	2.0 mg
Paclitaxel	6.0 mg
Absolute Alcohol	to 1.0 mL

The pH of this solution was determined as 6.1.

The stability of this sample was compared with a sample prepared by the formulation stated in the NCI Taxol Clinical brochure (as follows) which had a pH of 9.1. (Sample 2)

Sample 2	per mL
Paclitaxel	6 mg
Cremophor EL	0.5 mL
Absolute Alcohol	to 1 mL

The solutions were filled into clear type 1 glass 5 mL vials and sealed with rubber bungs.

The solutions were stored at 40° C for 7 (seven) days and the stability results are shown in Table 1.

	Sample 1	Sample 2
pH	6.2	9.0
Potency	96.6	86.7
Major individual impurity	0.3%	5.1%
Total impurities	1.0%	12.2%

Clearly Sample 1 showed significantly increased stability over Sample 2.

Example 2

[00018] A solution was prepared with the following formulation:

Formulation: (Sample 3)

Cremophor EL	0.5 mL
Paclitaxel	6.0 mg
Absolute Ethanol	to 1.0 mL

pH adjusted to 6.6 with 1.0M Acetic Acid.

The solution was filled into clear type I glass 5 mL vials and sealed with rubber bungs.

The solution was stored at 40° C for 7 days.

The stability results obtained are compared to those seen with Sample 2.

	Sample 3	Sample 2
pH	6.7	9.0
Potency	97.5	86.7
Major individual impurity	0.3%	5.1%
Total impurities	2.3%	12.2%

Again the significantly superior stability of the formulation according to the invention (Sample 3) is evident.

[00019] It will be clearly understood that the invention in its general aspects is not limited to the specific details referred to hereinabove.